

### **REMARKS/ARGUMENTS**

The amendments to the claims are fully supported by the specification and claims as originally filed and do not constitute new matter.

Prior to the present amendment, Claims 58-65 and 68-70 were pending in this application. With this amendment, Claims 58-62 have been amended to recite an "isolated native sequence polypeptide." Support for the term "native sequence" can be found in the specification at, for example, page 121, line 38 to page 122, line 11. A "native sequence PRO polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide" specifically encompasses "naturally-occurring truncated or secreted forms of the specific PRO polypeptide ... naturally occurring variant forms ... and naturally occurring allelic variants of the polypeptide."

Applicants believe that the current amendments place all claims in *prima facie* condition for allowance or, at least, in a better form for consideration on appeal. Accordingly, the consideration and entry of the present amendment after final rejection is respectfully requested.

Claims 58-65 and 68-70 are pending in this application.

The rejections of Claims 58-65 and 68-70 under 35 U.S.C. §§101 and 112, first paragraph, are addressed below.

#### **Claim Rejections Under 35 U.S.C. §§101 and 112, First Paragraph**

Claims 58-65 and 68-70 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

Claims 58-65 and 68-70 further remain rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility ..., one skilled in the art would not know how to use the claimed invention."

For the reasons outlined below, Applicants respectfully disagree and traverse the rejections.

## Utility – Legal Standard

According to 35 U.S.C. § 101:

Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added.)

In interpreting the utility requirement, in *Brenner v. Manson*<sup>1</sup>, the Supreme Court held that the quid pro quo contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, *i.e.*, a utility "where specific benefit exists in currently available form."<sup>2</sup> The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."<sup>3</sup>

Later, in *Nelson v. Bowler*<sup>4</sup>, the CCPA acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."<sup>5</sup>

In *Cross v. Iizuka*<sup>6</sup>, the CAFC reaffirmed *Nelson* and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results

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<sup>1</sup> *Brenner v. Manson*, 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

<sup>2</sup> *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

<sup>3</sup> *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

<sup>4</sup> *Nelson v. Bowler*, 626 F. 2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

<sup>5</sup> *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

<sup>6</sup> *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

with the particular pharmacological activity are generally predictive of *in vivo* test results, *i.e.*, there is a reasonable correlation there between."<sup>7</sup> The Court perceived "no insurmountable difficulty" in finding that, under appropriate circumstances, "*in vitro* testing, may establish a practical utility."<sup>8</sup>

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.<sup>9</sup> The PTO has the initial burden that applicants' claims of usefulness are not believable on their face.<sup>10</sup> In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."<sup>11, 12</sup>

Compliance with 35 U.S.C. §101 is a question of fact.<sup>13</sup> The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.<sup>14</sup> Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

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<sup>7</sup> *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

<sup>8</sup> *Id.*

<sup>9</sup> *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

<sup>10</sup> *Ibid.*

<sup>11</sup> *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (CCPA 1974).

<sup>12</sup> See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

<sup>13</sup> *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) *cert. denied*, 469 US 835 (1984).

<sup>14</sup> *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

The well established case law is clearly reflected in the Utility Examination Guidelines (“Utility Guidelines”),<sup>15</sup> which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted “specific, substantial, and credible utility” or a “well-established utility.” Under the Utility Guidelines, a utility is “specific” when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the “substantial utility” standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase “immediate benefit to the public” or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be “currently available” to the public in order to satisfy the utility requirement. “Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a “substantial” utility.”<sup>16</sup> Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement<sup>17</sup> gives the following instruction to patent examiners: “If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.”

#### **Proper Application of the Legal Standard**

The specification provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO351 polypeptide and antibodies binding to PRO351 for the reasons previously set forth in the Applicants' responses filed on July 15, 2004 and April 29, 2004 and below.

The Examiner alleges that “the specification provides data showing a very small increase in DNA copy number, approximately 2-fold, in a few tumor samples for PRO351. There is no

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<sup>15</sup> 66 Fed. Reg. 1092 (2001).

<sup>16</sup> M.P.E.P. §2107.01.

<sup>17</sup> M.P.E.P. §2107 II(B)(1).

evidence regarding whether or not the PRO mRNA or protein levels are also increased in these tumor samples.”

Applicants respectfully disagree and traverse the rejection.

First of all, Applicants respectfully submit that the gene amplification assay is well-described in Example 143 of the present application. The nucleic acids encoding PRO351 had  $\Delta C_t$  value of  $> 1.0$ , which is **more than 2-fold increase**, for primary lung tumors LT9, LT10, LT11, LT13, LT15, LT16, LT17, LT18, LT19 and LT21. Therefore, PRO351 showed approximately 1.02 to 1.46  $\Delta C_t$  unit which corresponds to  $2^{1.02}$  to  $2^{1.46}$  - fold amplification or 2.03 to 2.75 fold amplification in primary lung tumors. Therefore, Applicants respectfully submit that the PRO351 nucleic acid was amplified in a significant number of lung tumors and showed a significant increase in DNA copy number in these tumors.

For further support, Applicants submit a Declaration by Dr. Audrey Goddard with this response and particularly draw the Examiner's attention to page 3 of the declaration which clearly states that:

It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample **is significant** and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

The attached Declaration by Audrey Goddard clearly establishes that the TaqMan real-time PCR method described in Example 143 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. Therefore, any gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay is considered useful as a marker for the diagnosis of cancer. Accordingly, the facts disclosed in the Declaration confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO351 is *a diagnostic marker of human lung cancer*.

The Examiner asserts,

Pennica et al. was cited as evidence showing lack of correlation between gene (DNA) amplification and elevated mRNA levels. Konopka et al. was cited as evidence showing lack of correlation between gene amplification and increased protein levels. Haynes et al. was cited as providing evidence that protein levels cannot be accurately predicted from mRNA levels, and that variances as much as 40-fold or even 50 fold were not uncommon.

Applicants respectfully submit that for the reasons previously set forth in the Applicants' response filed on April 29, 2004 that Pennica *et al.* does not show a lack of correlation between gene (DNA) amplification and elevated mRNA levels in general.

Further, the Examiner cites the abstract of Konopka *et al.* to establish that "[p]rotein expression is not related to the amplification of the *abl* gene . . . ." Again, Applicants respectfully submit that the Examiner has generalized a result pertaining to merely **one** gene, the *abl* gene, to cover all genes in general. Konopka does not disclose any generalized teaching about the correlation between protein expression and gene amplification. Applicants submit that the Konopka reference is not sufficient to establish such a *prima facie* showing of lack of utility based on the results with the *abl* gene alone.

Thus, the combined teachings of Pennica and Konopka are not directed towards genes in general but to single gene or genes within a family and thus, their teachings have been misinterpreted in this rejection.

The Examiner cites the Haynes *et al.* reference to establish that "protein levels cannot be accurately predicted from the level of corresponding mRNA levels, and that, and that variances as much as 40-fold or even 50 fold were not uncommon."

As a preliminary matter, it is not a legal requirement to establish a "necessary" correlation between an increase in the copy number of the mRNA and protein expression levels. As discussed above, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, the question is not whether a necessary or even "strong" correlation between an increase in copy number and protein expression levels exists, rather if it is more likely than not that a person of ordinary skill in the pertinent art would recognize such a positive correlation. Applicants

respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Indeed, contrary to the Examiner's reading, Haynes teaches that "there was a *general trend but no strong correlation* between protein [expression] and transcript levels" (Emphasis added). Haynes studied 80 *yeast* proteins to show that protein levels (*i.e., protein amounts*) cannot be *accurately* predicted from the level of the corresponding mRNA transcript. (See page 1863, under Section 2.1, last line, emphasis added). For example, in Figure 1, there is a positive correlation between mRNA and protein amongst *most* of the 80 yeast proteins studied. In fact, very few data points deviated or scattered away from the expected normal or showed a lack of correlation between mRNA and protein levels (*i.e., an increase in mRNA resulted in a decrease in protein levels*).

In addition, the analysis by Haynes *et al.* is not relevant to the current application. Haynes was studying yeast cells and not human cells. Haynes *et al.* notes that their analysis focused on the 80 most abundant proteins in the yeast lysate. (See page 1867). Haynes *et al.* states that "since many important regulatory protein are present only at low abundance, these would not be amenable to analysis." (See page 1867). Further, Haynes *et al.* compared the protein expression levels of these naturally abundant proteins to mRNA expression levels from published SAGE frequency tables. (See page 1863). Accordingly, Haynes *et al.* did not compare mRNA expression levels and protein levels in the same yeast cells. Thus, the analysis by Haynes *et al.* is not applicable to the present application.

Applicants respectfully submit that the law does not require the existence of a "strong" or "linear" correlation between mRNA and protein levels. Nor does the law require that protein levels be "accurately" predicted. According to the authors themselves, the Haynes data confirm that there is a general trend between protein expression and transcript levels, which meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Therefore, Applicants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in Haynes *et al.*, and application of an improper, heightened legal standard. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is more likely than not that the encoded protein

will be expressed at an elevated level. As noted even in Haynes *et al.*, most genes showed a correlation between increased mRNA and translated protein.

The Examiner contends that "Orntoft *et al.* do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time.... Orntoft *et al.* concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p.40). This analysis was not done for PRO351 in the instant specification. That is, it is not clear whether or not PRO351 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance of Orntoft *et al.* is not clear." The Examiner further alleges, "Hyman *et al.* used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract).... Therefore, Hyman *et al.* also do not support utility of the claimed polypeptides." The Examiner alleges that "Pollack *et al.* also used CGH technology concentrating on large chromosome regions showing high amplification (p. 12965). Pollack *et al.* did not investigate polypeptide levels. Therefore, Pollack *et al.* also do not support the asserted utility of the claimed invention."

In Orntoft *et al.*, 1,800 genes that yielded an increase or decrease in mRNA expression in two invasive tumors compared to the two non-invasive papillomas were then mapped to chromosomal locations. The chromosomes had already been analyzed for amplification by hybridizing tumor DNA to normal metaphase chromosomes (CGH). Orntoft *et al.* used CGH alterations as the independent variable and estimated the frequency of expression alterations of the 1,800 genes in the chromosomal areas. Orntoft *et al.* found that in general (77% and 80% concordance) areas with a strong gain of chromosomal material contained a cluster of genes having increased mRNA expression (see page 40). Orntoft *et al.* state, "For both tumors TCC733 ( $p<0.015$ ) and TCC827 ( $p<0.00003$ ) a highly significant correlation was observed between the level of CGH ratio change (reflecting the DNA copy number) and alterations detected by the array based technology" (see page 41, column 1). Orntoft *et al.*, also studied the relation between altered mRNA and protein levels using 2D-PAGE analysis. Orntoft *et al.* state, "In general there was a highly significant correlation ( $p<0.005$ ) between mRNA and protein alterations.... 26 well focused proteins whose genes had a known chromosomal location were detected in TCCs 733 and 335, and of these 19 correlated ( $p<0.005$ ) with the mRNA changes detected using the arrays." (See page 42, column 2 to page 34, column 2). Accordingly, Orntoft



*et al.* clearly support Applicants position that proteins expressed by genes that are amplified in tumors are useful as cancer markers.

The Examiner indicates that Applicants have not indicated whether PRO351 is in a gene cluster region of a chromosome. (See page 6 of the instant Office Action). Applicants fail to see how this is relevant to the analysis. Orntoft *et al.* did not limit their findings to only those regions of amplified gene clusters. Further, as discussed below, Hyman *et al.* and Pollack *et al.* did gene-by-gene analysis across all chromosomes.

The Examiner has mischaracterized the methods used by Hyman *et al.* and Pollack *et al.* in their analysis. These papers did not use traditional CGH analysis to identify amplified genes. In Hyman *et al.*, 13,824 cDNA clones were placed on glass slides in a microarray and genomic DNA from breast cancer cell lines and normal human WBCs were hybridized to the cDNA sequences. For expression analysis, RNA from tumor cell lines were hybridized on the same microarrays. The 13,824 arrayed cDNA clones were analyzed for gene expression and gene copy number in 14 breast cancer cell lines. Hyman *et al.* state, "The results illustrate a considerable influence of copy number on gene expression patterns." For example, Hyman *et al.* teach that "[u]p to 44% of the highly amplified transcripts (CGH ratio, >2.5) were overexpressed (*i.e.*, belonged to the global upper 7% of expression ratios) compared with only 6% for genes with normal copy number." (See page 6242, column 1). Further, Hyman *et al.* state that "[t]he cDNA/CGH microarray technique enables the direct correlation of copy number and expression data on a gene-by-gene basis throughout the genome." (See page 6242, column 2). Therefore, the analysis performed by Hyman *et al.* was on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

In Pollack *et al.*, DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines was profiled. Pollack *et al.* further state, "Parallel microarray measurements of mRNA levels reveal the remarkable degree to which variation in gene copy number contributes to variation in gene expression in tumor cells." (See Abstract). "Genome-wide, of 117 high-level DNA amplifications (fluorescence ratios >4, and representing 91 different genes), 62% (representing 54 different genes; ...) are found associated with at least moderately elevated mRNA levels

(mean-centered fluorescence ratios >2), and 42% (representing 36 different genes) are found associated with comparably highly elevated mRNA levels (mean-centered fluorescence ratios >4)." (See page 12966, column 1). Therefore, the analysis performed by Pollack *et al.* was also on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

The Examiner also alleges that papers by Orntoft *et al.*, Hyman *et al.* and Pollack *et al.* "state that the research was relevant to the development of potential cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertion that the claimed PRO351 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial."

Applicants respectfully disagree.

As stated above, in explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility.'"<sup>18</sup> Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement<sup>19</sup> states, "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

Applicants have clearly shown that based upon the gene amplification results that there is a clear correlation between the amplification and overexpression of the PRO351 gene and lung tumors. Accordingly, Applicants respectfully submit that Applicants' assertion that the claimed PRO351 proteins have utility in the field of cancer diagnostics is substantial.

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<sup>18</sup> M.P.E.P. §2107.01.

<sup>19</sup> M.P.E.P. §2107 II(B)(1).

With regard to the correlation between mRNA expression and protein levels, Applicants previously submitted a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

The Examiner contends that Dr. Polakis Declaration is insufficient to overcome the rejection of claims 58-65 and 68-70 since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels and not gene amplification levels and protein levels. The examiner further alleges that only Dr. Polakis' conclusions are provided in the Declaration. Thus, the Examiner asserts that there is no evidentiary support to Dr. Polakis

statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide.

Applicants submit that Dr. Polakis' Declaration is presented to support the position that there is a correlation between mRNA levels and polypeptide levels. Regarding, the Examiner's rejection of the Polakis Declaration "for not being supported by evidence of record," Applicants emphasize that the opinions expressed in the Polakis Declaration, including the quoted statement, are all based on factual findings. Thus, Dr. Polakis explains that in the course of their research using microarray analysis, he and his co-workers identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Subsequently, antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels were compared. In approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells. Dr. Polakis' statement that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell" is based on factual, experimental findings, clearly set forth in the Declaration. Accordingly, the Declaration is not merely conclusive, and the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by one skilled in the art.

The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.<sup>20</sup> "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument."<sup>21</sup> Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why

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<sup>20</sup> *In re Rinehart*, 531 F.2d 1084, 189 USPQ 143 (CCPA 1976); *In re Piasecki*, 745 F.2d 1015, 226 USPQ 881 (Fed. Cir. 1985).

<sup>21</sup> *In re Alton*, 37 USPQ2d 1578, 1584 (Fed. Cir 1996) (quoting *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992)).

opinion evidence relating to a fact issue should not be considered by an examiner."<sup>22</sup> Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines<sup>23</sup> which states, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." The statement in question from an expert in the field (the Polakis Declaration) states that "it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell." Therefore, barring evidence to the contrary regarding the above statement in the Polakis Declaration, this rejection is improper under both the case law and the Utility guidelines.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis Declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO351 gene, that the PRO351 polypeptide is concomitantly overexpressed. Thus, Applicants submit that the PRO351 polypeptides and antibodies have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the claimed polypeptides for diagnosis of cancer.

The Examiner cites Hu *et al.* for support that genes displaying a 5-fold change or less in mRNA expression in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease.

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<sup>22</sup> *In re Alton, supra.*

<sup>23</sup> Part IIB, 66 Fed. Reg. 1098 (2001).

Applicants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Accordingly, contrary to the Examiner's assertion, Applicants respectfully submit that Hu *et al.* does not conclusively show that it is more likely than not that the gene amplification does not result in increased expression at the mRNA and polypeptide levels.

First, the title of Hu *et al.* is "Analysis of Genomic and Proteomic Data Using Advanced Literature Mining." As the title clearly suggests, the conclusion suggested by Hu *et al.* is merely based a statistical analysis of the information disclosed in published literature. As Hu *et al.* states, "We have utilized a computational approach to literature mining to produce a comprehensive set of gene-disease relationships." In particular, Hu *et al.* relied on MedGene Database and the Medical Subject Heading (MeSH) files to analyze the gene-disease relationship. More specifically, Hu *et al.* "compared the MedGene breast cancer gene list to a gene expression data set generated from a micro-array analysis comparing breast cancer and normal breast tissue samples." (See page 408, right column).

Therefore, Applicants submit that the reference by Hu *et al.* only studies the statistical analysis of micro-array data and not the gene amplification data. Hence, their findings would not be directly applicable to the gene amplification data. In addition, the Hu *et al.* reference does not show a lack of correlation between microarray data and the biological significance of cancer genes.

Further, the analysis by Hu *et al.* has certain statistical flaws. According to Hu *et al.*, "different statistical methods" were applied to "estimate the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). It is well known in the art that various statistical methods allow different variables to be manipulated to affect the outcome. For example, the authors admit, "Initial attempts to search the literature using" the list of genes, gene names, gene symbols, and frequently used synonyms, generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors further admit that the false positives caused by

"duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* (emphasis added). Hence, Applicants respectfully submit that in order to minimize the false positives and negatives in their analysis, Hu *et al.* manipulated various aspects of the input data.

Applicants further submit that the statistical analysis by Hu *et al.* is not a reliable standard because the frequency of citation only reflects the current research interest of a molecule but not the true biological function of the molecule. Indeed, the authors acknowledge that "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). It often happens in the scientific study that important molecules were overlooked by the scientific society for many years until the discovery of their true function. Therefore, Applicants submit that Hu *et al.* drew their conclusion based on a very unreliable standard and their research does not provide any meaningful information regarding the correlation between the microarray data and the biological significance.

Even assuming that Hu *et al.* provide evidence to support a true relationship, the conclusion in Hu *et al.* only applies to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and can not be generalized as a principle governing microarray study of breast cancer in general, let alone the various other types of cancer genes in general. In fact, even Hu *et al.* admit that "[i]t is likely that this threshold will change depending on the disease as well as the experiment. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column). Therefore, based on these findings, the authors add, "This may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (Emphasis added).

Accordingly, Applicants respectfully submit that the Examiner has not shown that a lack of correlation between microarray data and the biological significance of cancer genes.

In conclusion, Applicant submits that the present rejection is based on the application of an incorrect, elevated legal standard, on misconstruction of the references and erroneous

conclusions drawn therefrom. The issue of patentable utility should be assessed on the totality of evidence, using the preponderance evidentiary standard. It is submitted that on the totality of evidence Applicants clearly established that the claimed invention has a substantial, specific and credible utility. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed polypeptides. Accordingly, Applicants request the Examiner to reconsider and withdraw the rejection of Claims 58-65 and 68-70 under 35 U.S.C. §§101 and 112.

### **CONCLUSION**

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2630 P1C10**).

Respectfully submitted,

Date: May 20, 2005

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